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1. Litchfield, H. R.: Archives Pediatrics 74:463, 1957

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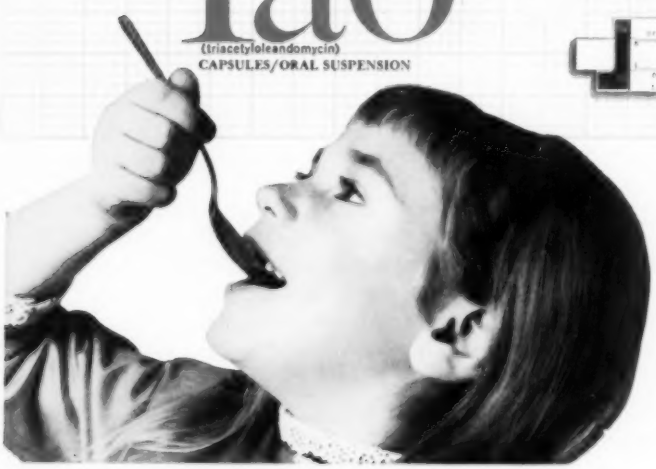

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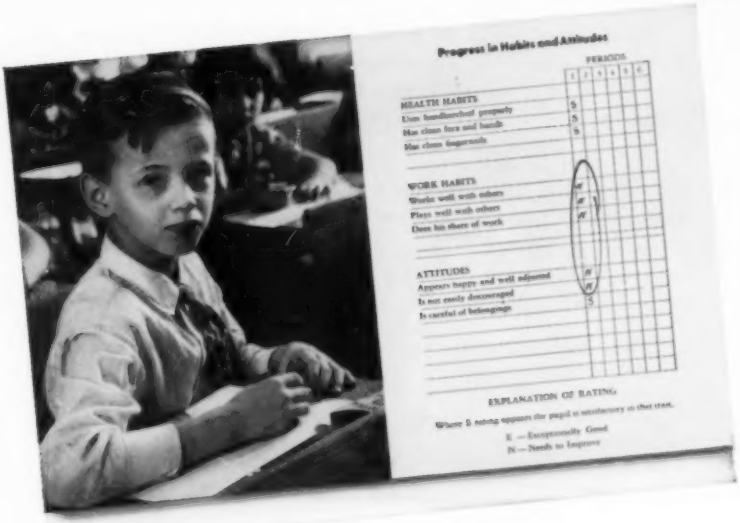

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THE PROBLEM OF ENDOCARDIAL FIBROELASTOSIS

H. LEHNDORFF, M.D.*

New York

The discussion of endocardial fibroelastosis should start with a generally accepted definition. *Gowing*[1] states: "Fibroelastosis of the endocardium is a congenital condition of unknown etiology in which there occurs a diffuse thickening of the mural endocardium associated with myocardial hypertrophy and leading to early death." And *Robbins*[2] in the modern Textbook on Pathology (1957) states: "Endocardial fibrosis is a not uncommon heart disease of obscure etiology".

In striking contrast to such modest statements are the numerous hypotheses. I feel that the name itself "endocardial fibrosis" was partly responsible for the difficulty in gaining a satisfactory understanding. The term expresses the astonishment felt by observers on finding whitish membranes covering the ventricular wall like an icing, instead of the normal brownish red, smooth surface. The term sounded well, indeed too well, and induced a pattern of thinking about the disease and an easy explanation of its pathogenesis; it was assumed[3,4], to be a special type of congenital heart malformation resulting in myocardial hypertrophy and finally causing heart failure. The endocardial lesion was supposedly the primary lesion, the myocardial hypertrophy a secondary manifestation.

The fact that endocardial fibrosis was observed in new born and young infants led to the conclusion that the disease must have started prenatally in utero — an embryopathy. Immediately the question arises as to which factors might cause the maldevelopment of the fetal heart. There are two possibilities: an alteration of the genes, a deterioration or defect of the germ plasma—the intrinsic

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factor.[5,6,7,8] Another hypothesis assumes obnoxious agents transmitted via placenta from the mother: the extrinsic, environmental factor. The occurrence of endocardial sclerosis in siblings in the same family and the finding of identical types of congenital heart malformations in three generations of a family—parents, children and grandchildren—can be taken as supporting evidence for the genetic theory.[6,7,9] Nevertheless this is not convincing evidence: identical environmental factors might be active in every subsequent pregnancy.

Evidence for the environmental agents is largely negative. In hundreds of cases observers have stressed the perfect health of the mother, the undisturbed pregnancy and delivery. There is a single case of rubella in early pregnancy reported[10] and one of infectious mononucleosis, which might point to transplancental transmission of a virus damaging the development of the fetal heart. However, during a severe epidemic of rubella in Australia, in which a number of babies were born with retrolental fibrosis as well as with cardial malformations there were septal defects, patent ductus arteriosus etc., observed but not a single case of endocardial fibrosis.[11]

Whether we prefer to consider the etiology as a genetic anomaly or an acquired disease, certain embryologic facts must be kept in mind. The gradual development and formation of the fetal heart can be disturbed only during the early phase of pregnancy (8-10 week), the "active" period of the rotation of the primary truncus. This process is extremely complicated and it must be controlled and regulated by a number of mechanisms which guarantee the normal development, the formation of the ventricles, atria and valves. The nature of these regulating factors and their ways of action is not known. I am inclined to speculate and assume the factor to be maternal hormonal substances, abundantly present during pregnancy, and, perhaps, particularly "growths hormones", indispensable for the development of the fetal organs. Obviously any disturbing factor acting during the active phase of heart formation could produce malformations of the fetal heart. In animal experiments, heart abnormalities could be produced by exposing the pregnant mother animal to malnutrition, especially vitamin deficiency, anoxia, X-ray irradiation and other harmful procedures.[12,13] Among the malformations, septal defects, retarded occlusion etc. were found, but, as far as I know, not a single observation of endocardial fibrosis. Anyhow, data obtained from experiments on rats and mice can not be extrapolated as an explanation

for the pathogenesis of heart anomalies in the human fetus.

The mothers of infants with endocardial fibrosis were not exposed to irradiation, and did not suffer from toxemia in early pregnancy or other demonstrable disturbance of health. But there is a factor, largely overlooked, which could play a role in the pathogenesis; the psychic trauma. For centuries folklore assigned an important role to maternal emotional disturbances, which might have a damaging effect on the fetus: anxiety and worry arising from the fact of having become pregnant, fear of delivery pain, economic distress and others.[14] They all cause "stress" and stress may conceivably lead to hormonal imbalance. True, this hypothesis is not proven, but, faced by a phenomenon, which has defied explanation one hypothesis is better than none, especially if it suggests a new approach for research.

During the past decade investigations have convincingly demonstrated two factors which could cause the excessive growth of the fibroelastic tissue in the subendocardial layer, i.e. the condition we call endocardial fibroelastosis: they are trauma and anoxia.

Trauma: Anderson and Kelly[7] have convincingly demonstrated the role of trauma in congenital heart malformations. Fibroelastic thickening develops in areas exposed to permanent increased intracardial pressure, or traumatized by "jet effect", produced by spurting of the blood stream through septal defects or by chronic vibration of deformed valves. The extent and severity of the fibrosis and the cardial volume by hypertrophy and dilatation increases with the duration of the cardiac disease. This suggests a consideration of endocardial fibrosis as a progressive condition.[10] (Fig. 1.)

Anoxia: Anoxia has been held by *Johnson*[15] and others to be the most important causative factor. More recently it is considered to be an additional factor, rather than the primary one.[19] Blocking of blood circulation through the Thesbesian vessels by the fibrotic membrane may produce ischemia in the myocardium and become a contributory cause of the final heart failure; delayed and insufficient emptying of the left ventricle may lead to stagnant hypoxia.

Although we know that trauma and anoxia during intrauterine life can lead to overgrowth of the fibroelastic tissue in the subendocardium, this knowledge does not solve the problem; in other words our present knowledge answers the question about the mechanism of fibroelastosis but not its basic cause.

The fact that endocardial fibroelastosis has been observed in

different types of heart disease induced the concept of considering it no longer as a morbid entity, but rather as the manifestation of overgrowth of the fibroelastic connective tissue in the subendocardial layer, a reaction to irritant agents as trauma or anoxia. But even this now generally accepted hypothesis can only explain the mechanism, but not the cause: the "how" but not the "why". It seems most probable to look for a primary alteration in the fetal

Fig. 1 A

Fig. 1 B

Fig. 1 C

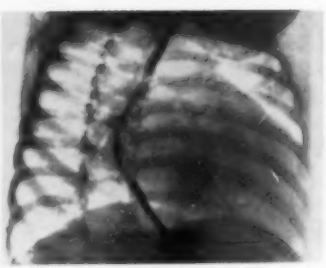

Fig. 2

Fig. 1. Demonstrating the gradual increase of the heart silhouette. a) 6 days old, considered normal in size; b) 3 months of age; c) 6 months old, ante mortem. *From Prec and Cassels.* Functional aspects of congenital defects. J. Paediatr. 41: 451, 1952.

Fig. 2. Roentgenogram demonstrating the deviation and compression of the barium-filled esophagus by the extremely dilated left atrium. *Prior and Wyatt:* Endocardial fibroelastosis Am. J. Path 26: 969, 1950.

heart muscle. I agree with Black-Schaffer[16] who states: "A reasonable hypothesis may begin with the postulate, that the basic factor must be sought in the myocardium". The concept of a congenital, constitutional and histologically demonstrable anomaly of the heart muscle sounds convincing. An abnormity of the myocardial fibrils would imply weakness and diminished resistance and

form a predisposing condition, on which damaging agents will produce excessive growth of the subendocardial connective tissue; the postnatal increased intraventricular pressure will cause dilatation of the heart; endocardial fibrosis can be formed in any weak and dilated heart.

The nature of the basic alteration of the myocardium has not yet been established: it could be assumed to be an *inherited defect* or a *disorder acquired* during the intrauterine life; the majority of pediatricians believe that the causative factor is a genetically defined disorder of the metabolism.

Histologic studies have revealed evidence of such a primary abnormality of the heart muscle. It has been found in cases of endocardial fibroelastosis with heart enlargement, that the muscle fibers are increased in number but not in volume; more fibers and more nuclei were counted in a given field of vision. That indicates that there is "*hyperplasia and not hypertrophy.*" Therefore the basic disorder in endocardial fibrosis is a "*myocardial dysplasia*".[17]

Another important result of histologic studies is the demonstration that excessive growth of fibroelastic tissue is often not restricted to the endocardium; identical hyperplasia of the connective tissue has been seen in the adventitia of capillaries and arterioles in branches of coronary vessels as well as on capillaries in liver, pancreas, ovaries, mesentery and other organs.[5,18] Such observations support the concept of endocardial fibroelastosis as the cardial localization of a generalized, systematic cardiovascular disease. These important findings need to be confirmed by further investigations.[19]

CLASSIFICATION

Fibrotic thickening of the endocardium has been observed in varying degree in a variety of heart affections. It seems advisable to separate—at least for didactic reasons, different types.

A. The *idiopathic, congenital endocardial fibroelastosis*, a relatively small group, in new born and young infants, characterized by the absence of any other cardial abnormality; the thick white mural membrane is the only manifestation.

B. The group of *well defined heart malformations;* the fibrosis—not at all obligate—appears in spots exposed to traumatization.

C. The *transitional forms.* The fibroelastosis is not restricted to the wall of the ventricle; papillary muscles are involved result-

ing in flattening and shortening. Involvement of the valves causes deformation and some degree of insufficiency or stenosis. These types could be taken either as an intensification of the idiopathic form or may be considered as a special type of cardiac malformation.

D. The large incongruent group of fibroelastosis in *myocarditis*, caused by bacterial or virus infections, on the basis of allergy or malnutrition, vitamin deficiency and some of unknown etiology. In this group belong the cases in adults and the African endomyocarditis.

E. Rare observations of endocardial fibroelastosis in the so-called *"myocardoses"*; congenital abnormalities of the myocardium, metabolic disorders of genetic origin: e.g. van Gierkes glycogen disease, gargoylism and others. On rare occasions endocardial fibrosis accompanies these conditions.

The term "Endocardial fibroelastosis", or fibrosis or sclerosis is generally accepted but nevertheless not quite correct and misleading. Recently *Black-Schaffer and Turner*[17] suggested "Congenital infantile myocardial dysplasia with endocardial fibrosis" and *Lambert and Vlad*[19] considered the affection as one type of "Primary endomyocardial diseases". Better understanding of the pathogenesis will lead to a more correct nomenclature.

DIAGNOSIS AND TREATMENT

A few remarks about diagnosis and treatment are in order. For a long time endocardial fibrosis was a "post-mortem" diagnosis. Of course, there are no pathognomonic signs, no decisive laboratory findings. Nevertheless, in many cases the condition may be recognized in vivo. The number of correctly diagnosed cases increases with the physicians awareness. Confronted with a young infant in respiratory distress with signs of left heart failure, or with signs of a congenital heart malformation, by absence of permanent cyanosis and distinctive murmurs by repeated examination, a tentative diagnosis of endocardial fibroelastosis is indicated. The dominant signs, tachycardia, dyspnea, cough, vomiting are in themselves not diagnostic. But it is the "music," the peculiar noises which accompany them. They are described as gargling, snoring, wheezing, grunting, quite different from any noises we are used to hearing in any respiratory disease in infants.

Radiology provides another important diagnostic manifestation; enlargement of the left atrium compressing and deviating the

trachea as oesophagus. This offers a satisfactory explanation for the peculiar respiratory noises, the persistent hacking cough and the intractable vomiting.[20] The routine *treatment* of acute heart failure is often effective but only temporarily and there is no way to predict which child will react favorably and how long the recovery will last. Recently Rossi[21] and others reported astonishing results with ACTH and cortisones, even complete recovery. Far more experience is necessary before these optimistic reports can be accepted. Surgery seems to become a promising type of treatment. Paul and Robbins[22] using Thompson's[23] cardiopericardiopexy technic reported very satisfactory results; the simple "poudrage operation", putting sterile talcum powder on the surface of the ventricle producing a granulation tissue has been performed in a number of infants: many are in good health after years, no longer have attacks of heart failure and lead a more or less active life without supporting digitalization. More observations are necessary; but even if the operation can not cure the anatomic alteration, it may prevent attacks of cardial insufficiency and permit a quiet life. But I feel skeptical about reports of complete healing after clinically observed repeated attacks of heart failure. If such a child remains in perfect health, there is no way to tell whether the disease was endocardial fibroelastosis or—more probably—an acute myocarditis.

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A monograph on Endocardial fibroelastosis will be published in Vol. XII, N. F. Ergebnisse der Inneren Midizin und Kinderheilkunde (in German) reviewing present knowledge with a list of approximately 250 references.

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THE ENURESIS PROBLEM

ROALD RINVIK AND JENS STEEN *

Norway

Enuresis is repeated involuntary passage of urine after the fourth year of life. Anatomical changes in the urinary tract or in the spinal nerves which result in lack of control of micturation are not included here. Most children are bladder trained during the night except for an occasional lapse between the age of 2 to 2½ years. Enuresis occurs in 12-15% of boys,—not so frequently in girls.

The large majority of these children wet their bed every night,—some several times and it is unusual that their bed is dry for more than a couple of nights in succession. Some of them also show day wetting besides—or exclusively day wetting takes place. The main part of the enuresis symptom is urgency. Well known is the special type of child who has an irresistible urge to empty its bladder immediately but manages to keep dry.

Enuresis is not exactly invalidizing but the condition is a stress for the child and not least for the parents. It might be a result of physical illness and can follow psychogenic or environment disturbances. But in the large majority of cases it is probably a developmental abnormality.

From an etiological point of view anatomical changes in the urinary tract are of minor importance, even though an infection might be the beginning of the symptoms. However, recent uretero-cystographic roentgen examinations (Fischer, Forsythe, Kjellberg) announce urinary tract changes in 20-40% of enuretic children. The most frequent finding in boys were valves in the posterior urethra; in girls, wide bladder neck anomalies and neurogenic bladder.

Epilepsy seems very rarely to be connected with the enuresis problem. In imbeciles, the frequency of enuresis is about 13%, but ordinarily mental retardation is not a prominent factor. Enuresis occurs among primitive people as well as in civilized societies.

Many authors stress the connection of emotional disturbances and behaviour changes and nervous symptoms on one side and enuresis on the other. Sometimes enuresis undoubtedly is a sign of emotional tension, but it is very difficult to decide if there is such an etiologic cause in individual cases. Abnormal electro-encephalographic tracings have been obtained in a large proportion of children with enu-

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resis. Some investigators have also found a high frequency of signs of psychogenic immaturity,—others an extremely deep sleep etc. All these signs might indicate that enuresis—at least in some instances —is part of disturbances in the cerebral function. Environmental factors might also play an important part, e.g. a separation from the mother,—a newborn infant in the family might be the reason why a formerly dry child suddenly starts wetting its bed.

In the large majority of the cases there is a family history of enuresis in one or both parents and in siblings. Socio-economic factors are also contributing in an important way as some find enuresis more frequent in the lower groups of the society. *Hallgren* has made a systematic genetic family analysis where he tries to control the influence of exogenic factors. His conclusion is that there probably exists one primary form of enuresis which has lasted since birth. This is a hereditary form compared to the secondary enuresis which often appears when the child primarily has been dry for about one year and then begins wetting. Otherwise it has not been possible to show any connection between the clinical picture of enuresis and the hereditary occurence of the symptom.

The analysis of our material of enuresis for the years 1951-1957 is as follows:

TABLE 1

Admitted	Boys 119	Girls 67	Total 186
Socio-economic status			
Worker	42	24	66
Employee	40	26	66
Independent	32	12	44
Unknown	5	5	10
Psychogenic "changes"			
In home	23	9	32
At School	4	4	8
			40—22%
Mentaly retarded	9	3	12— 6.45%
Follow up interviews answered	79	43	122
Heredity:			
Siblings	15	8	
Parents	20(6)	14(3)	
Other persons in family	16(4)	11(5)	
Enuresis in family	41	25	66
	51%	58%	54%

(The figures in parentheses show the contemporary occurrence in the previous group).

The socio-economic status does not seem to play any important part here as the patients are rather equally distributed from the different groups of society. (Table 1) About one fifth show some psychogenic changes and they are mainly when the children are in their homes. However, the estimation of this question is only based upon the impression the pediatrician has of the patient, his relations and the environment. We have not tried to make a psychological-psychiatric evaluation. The figures would probably have been much greater if the estimation had been done by a doctor especially educated and interested in psychiatric problems. Intelligence tests have not been performed on these children. The daily contact during some weeks has given the impression of completely normal intelligence. However, 12 patients, i.e. 6.45% were mentally retarded.

A follow-up interview was answered by 122 of the 186 patients admitted. The hereditary factor was confirmed as every other patient gave information about one or more members in the family with the same difficulties.

Of 159 patients examined with EEG, (Table 2) more than one-fourth—40 patients have abnormal EEG* tracings,—mainly as dysrythmias. Epileptogenic reactions are very rare. Some investigators claim that EEG gives a basis to decide the prognosis of the enuresis, children with EEG changes are supposed to maintain their troubles longer than those with normal EEG tracings. Our estimations of the patients where enuresis continues show very small differences between those with and those without EEG changes.

TABLE 2

EEG-examinations:

	Boys	Girls	Total	
"Abnormal" EEG	28	12	40	25%
Normal	75	14	119	
EEG not done	16	11	27	

The *prognostic value* of EEG:

	Cured after hospital stay	Cured later	Enuresis cont.	
"Abnormal" EEG 26 patients	1	9	16	61%
Normal 81 patients	17	18	46	56%

X-ray examinations of the urinary tract (urograms) have been performed on 158 patients and anomalies were found in 9 patients, i.e. 5.7%. This figures is considerably lower than those announced in recent publications mentioned above. Newer X-ray technique (uretero-cystograms,—examination during micturation) might dis-

*The EEG's examined by Birger Kaada, M.D.

close more values etc. But are examinations like these justified as routine? We believe not. Surprisingly many of our patients become dry shortly after admission and keep dry during the hospital stay. When they are back home the wetting starts anew. It is very unlikely that these children have organic anomalies in the urinary tract. X-ray examinations in this region, partly of long duration, will without doubt also increase in girls the radiation risk considerably.

TABLE 3

X-ray examinations of the urinary tract

	Boys	Girls	Total	
Changes	4	5	9	5.7%
Normal	99	50	149	
Not done	16	12	28	
			186	

Anomalies: 4 boys: 2 doubled ureter and plevis
1 dilated pelvis
1 stricture of ureter and dilatation.
5 girls: 2 doubled ureter and pelvis with ectopic ureter.
1 doubled ureter and pelvis
1 diverticulus vesicae.
1 "kinked" ureter with passage difficulties

TREATMENT

The stay in the hospital has been of variable length depending on the availability of beds etc. We have stressed a thorough examination partly for psycho-therapeutical reasons and the patients have been put on a certain regime where they also have been awakened once every night. Drugs have been used only occasionally.

Our follow-up interviews show that only 24 of 122 are claimed to be cured after the stay, i.e., about one fifth. 21 patients or 12% are announced cured later, but 77 patients or 63% are still wetting 1-6 years after hospitalization:

TABLE 4

	Boys	Girls	Total	
Cured after hospital stay	16	8	24	19.7%
Cured afterwards	10	11	21	17.2%
Enuresis continued	53	24	77	63.1%

Considering the time and expense of hospitalization the result is very depressing. In the last few years we have found that the main reason for hospital admission probably is to exclude any organic basis for enuresis. Before the patient is 5-6 years old hospitalization is probably of little use. Of course anomalies of the urinary tract

can be found before that age by X-ray examinations, but no psychological effect of the admission could be expected. That is at least one point to remember. Awakening the patient once at night is perhaps the most important detail of the regime, but it is of the greatest importance that the child really is awake. He must catch the meaning and understand what it's all about,—then he can cooperate and voluntarily empty his bladder. It is probably of no use to reduce drinking in the afternoon as these children will drink secretly if they are forbidden. There exists no drug with definite effect. For many years belladonna has had a good reputation, but it should be given for a long time and in sufficient quantities. Belladonna lowers the bladder tension and pressure by reducing the contraction and thus increasing the capacity of the bladder. Children ordinarily tolerate belladonna very well, but now and then one finds toxic reactions which eventually are not serious. Rashes, dryness in the skin and dilatation of the pupils are the most common signs which indicate lowering of the dose.

The most important part of the treatment, however, probably is to get the parents to understand the difficulties of the child with enuresis and adjust themselves and the child accordingly for the duration of the ailment.

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STUDIES ON THE PHYSIOLOGICAL ACTIVITY OF LACTOBACILLUS BIFIDUS

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In 1899, Tisser[1] reported that the normal intestinal flora in the infant was basically different from that in the adult. He showed that in the breast-fed infant, Lactobacillus bifidus, which is anerobic, forms the major part of the normal intestinal flora. This bacillus has been treated as a sort of a step-child by the bacteriologist, perhaps due to the fact that it is non-pathogenic. It has however, been considered important and studied widely by pediatricians. With the object of producing a milk preparation which would be similar in value to breast milk, efforts have been made to prepare products which would stimulate the growth of the Lactobacillus bifidus. The foundation for this is the fact that despite the small difference in growth promotion, susceptibility to disease and mortality between the artificially-fed and breast-fed infant in recent years parallel with improvement in milk products, the superiority of breast milk still cannot be denied. For example, it is well known that even though utilization of cow's milk protein is equal to that of breast milk, weight increase is poorer with cow's milk than with human milk when an equal quantity of protein is given. Moreover, there is little difference in the amino acid content and biological value in the protein between human and cow's milk. It was only natural therefore to try to explain the superiority of human milk by the difference in intestinal flora and pH. Bessau[2] has stated that the bifidus flora is the most physiological state in the infant and suggests that a pathological condition already exists bacteriologically when bifidus is decreased and coli predominates. The pediatrician therefore, attempted to convert the intestinal flora of bottle-fed infants to a bifidus dominant one. The addition of massive amounts of β-lactose in milk preparations as a manifestation of this. In 1948, Petuely[3-5] reported the presence of a bifidus enhancing substance in human milk and since then, numerous studies have been conducted on this so-called bifidus factor. The brilliant studies of Kuhn,[13-15] György,[6-12] Petuely, and others have demonstrated that although

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the method of handling the bifidus factor and the substance studied appears to differ according to each investigator, the final objective, i.e., conversion of the intestinal flora of infants to a bifidus flora, is the same.

We believe however, that this line of thought is too bold a leap as the physiological significance of the Lactobacillus bifidus has not yet been clarified and the reason why this bacillus is dominant in the intestinal flora of breast-fed infants is not clear. It can be readily understood that proliferation of the bifidus is accelerated by the bifidus factor present in breast milk but it has not been explained why it is beneficial in altering the intestinal flora by administration of cow's milk products. A review of the literature up to the present merely suggests that the intestinal content is acidified by proliferation of Lactobacillus bifidus and in so doing, inhibits growth of shigella, typhoid, coli and other pathogenic bacteria as well as putrifying bacteria.

Examination of protein utilization by using the bifidus factor has been reported by Adam. He divided the subjects into three groups, that is, healthy breast-fed infants, healthy cow's milk-fed infants and healthy bifidus-supplemented milk-fed infants and measured the free amino acid of the urine and feces. It was found that in the breast-fed infant, the amino acid content of the urine was low and that of the feces was high, whereas in the cow's milk-fed infant, this relation was reversed and the findings in the bifidus-supplemented milk-fed infant were similar to those in the breast-fed infant. From this, it was concluded that protein metabolism procedes smoothly when there is proliferation of Lactobacillus bifidus in the intestines and that supplementation of bifidus is vital for proper utilization of protein.

We have been conducting studies on the physiological significance of the Lactobacillus bifidus from an altogether different approach. Findings of interest are presented here for appraisal.

MATERIALS AND METHODS

1. Lactobacillus bifidus: Isolated from fresh samples of stool of breast-fed infants under anaerobic conditions (yellow phosphorus) and cultivated on liver extract; Hayward's medium added for 48 hours.

2. Lactobacillus acidophilus: Standard WHO strain maintained in the Institute for Microbial Diseases, Osaka University. Cultivated for 48 hours as above.

3. Bovine Lactobacillus bifidus: Isolated from stool samples of nursing calves 25 days after birth or younger, and cultivated for 48 hours as above.

4. Preparation of Lactobacillus bifidus enzyme fraction: Suspensions of human and bovine Lactobacillus bifidus were prepared with 0.5 M NaCl and adjusted to D5500=0.80 with the Coleman Jr. spectrophotometer. The suspension was then treated for one hour in the Mickles' desintegrator, equivolume of 0.5 M NaCl (adjusted to pH 8.1 with acetate buffer) added and centrifuged at 5,000 rpm for 15 minutes. The supernatant residue was used as the crude extract. Ammonium sulfate was added to the crude extract to 0.75 saturation, the precipitate redissolved in 0.5 M NaCl, dialysed for 78 hours against 0.5M NaCl and the contents of the inner bag lyophilized. This was called Fraction A and it remains stable for two weeks in the powder form without loss of enzyme activity.

Fraction A was dissolved in 0.3 M NaCl in a concentration of 5%, dialysed for 48 hours against a large quantity of distilled water, the precipitate separated by centrifugation and redissolved in 0.5 M NaCl. The pH of this solution was adjusted to 5.2 and ammonium sulfate added to a final concentration of 0.6 saturation. The precipitate was collected by centrifugation, dialysed against distilled water for 72 hours and lyophilized. A white powder was obtained. This was called Fraction B. All the above procedures were carried out at temperatures below 4° C

5. Preparation of α-casein of Human and Cow's Milk: The α-casein of both human and cow's milk was prepared according to the same method unless otherwise specified. Milk was cooled to 2° C immediately after collection, the fat removed and adjusted to pH 4.6 with 0.1 N HCl. The skimmed milk was diluted to 5 times its volume with distilled water, (chilled to 2° C), left standing for about 3 hours and then centrifuged. The precipitate was redissolved in distilled water of pH 6.5 and extracted twice with ether and then diluted so as to contain 0.5% protein as the nitrogen. The pH was adjusted to 4.6 with 0.01 N HCl and the precipitate lyophilized. This was the crude casein.

The crude casein was dissolved in distilled water to make a 1% solution, adjusted to pH 6.5 with 0.1 N NaOH, shaken for several hours at 2° C and the pH then adjusted as quickly as possible to 3.5 with 0.05 N HCl. The precipitate was dissolved in distilled water so as to make the protein content 0.2-0.3% and 0.01 N NaOH dropped until the pH was neutralized to 6.2. This procedure was

repeated 7 times and the final precipitate lyophilized. A white powder was obtained. Above is a modification of the method of R. C Warner.

The α-casein fraction obtained by this procedure however, contains a small amount of β-casein so zone electrophoresis with the starch volumn was conducted in order to obtain a more purified α-casein. The casein was placed with borate buffer (pH 8.6, ionic strength 0.1) at the top of a 40 cm starch column of 5cm diameter and an electric current of 500V, 20mA run for 24 hours at a temperature of 2° C. The column was then transferred to the fraction collector.

Borate buffer (pH 8.6, ionic strength 0.1) was used as the effluent and 2ml aliquots collected. The protein content of each effluent was measured with the Folin reagent and it was found that α-casein was collected in the 28–72 ml effluent volumes. The effluents in this range were collected, dialysed against distilled water and lyophilized. A white powder was obtained and it was found that this was a single substance electrophoretically. This was used as the substrate in the experiments.

6. Quantitative Determination of Inorganic Phosphorus and Total Phosphorus: The Fiske and Subbarow method was used for measurement of the phosphorus.

7. Enzyme Activity Unit and Activity Rate: The quantity of enzyme liberating 1 mcg of inorganic P in 1 minute from a reaction mixture containing α-casein (contains 20mM casein P) at pH 6.1 and 31° C was taken as 1 unit and the rate of activity was expressed as the unit/mg protein nitrogen.

Buffer Solution: Unless otherwise specified, the Michaeli's veronal acetate buffer was used in all the experiments

RESULTS

1. Action of Enzyme Fractions of Lactobacillus Bifidus on α-casein of Human and Cow's milk.

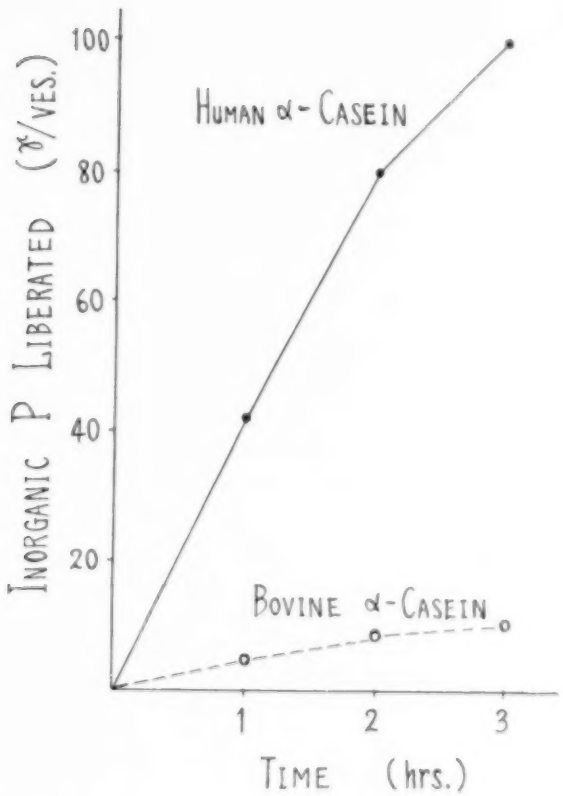
In all the experiments, the reaction mixture was composed of the following unless otherwise specified.

a. α-casein solution (contains 20mM casein P)	1.0ml
b. 4% solution of bifidus enzyme fraction	0.75ml
c. Veronal acetate buffer	0.25ml

Reaction of Fraction A with α-casein of human milk at 37° C results in the liberation of large amounts of inorganic P. When cow's milk α-casein is used as a substrate however, only a small

amount of inorganic P is liberated. In other words, the bifidus in this experiment was that isolated from the stool of a breast-fed infant and it can be seen that a type of phosphatase which acts specifically on α-casein of human milk is present in this bacillus.

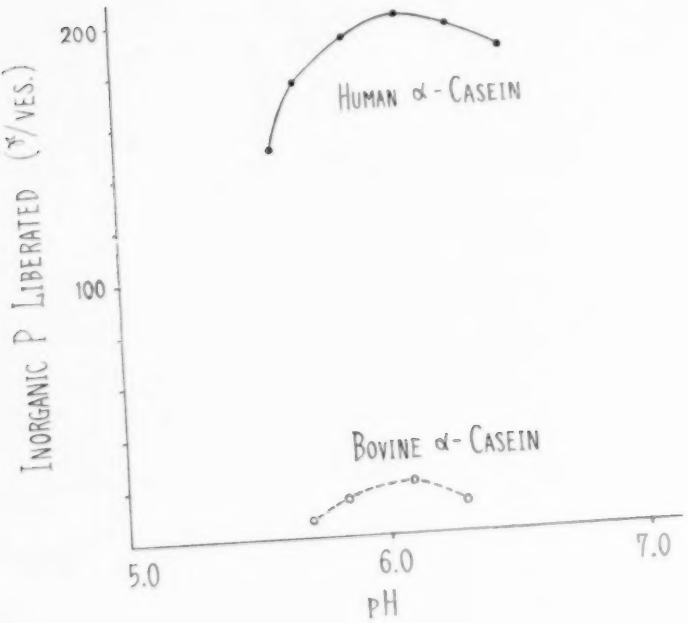
FIG. 1



2. Optimum pH of the Lactobacillus Bifidus Phosphatase.
The optimum pH for liberation of inorganic P by Fraction A

was determined. The reaction time was 10 hours. As shown in the chart, pH 6.1 was found to be optimal.

FIG. 2



3. Activity of the Various Enzyme Fractions.

Comparison of the activity of the enzyme fractions shows that Fraction B is 40 times purer than the crude extract.

	Units	*Activity*
Crude Extract	128.3	0.98
Fraction A	15	6.1
Fraction B	3.4	42.3

4. Effect of Oxidizing and Reducing Agents.

The effect of oxidizing and reducing agents on the phosphatase activity of the bifidus enzyme fraction was examined. Ascorbic acid,

cysteine, and thioglycollic acid were used as the reducing agents and hydrogen peroxide and ferric chloride were used as oxidizing agents. As can be seen in the table, a marked rise in phosphatase activity was found with addition of reducing agents while an inhibition occurred with oxidizing agents.

	Agent	Inorganic P Liberated
Oxidizing Agents	Ascorbic acid (0.0015 M)	240
	Ascorbic acid (0.001 M)	206
	Cysteine (0.01 M)	225
	Cysteine (0.001 M)	143
	Thioglycollic acid (0.01 M)	184
	Thioglycollic acid (0.001 M)	173
Reducing Agents	Hydrogen peroxide	101
	Ferric chloride	43
No addition		103

5. Specificity of Phosphatase Activity.

A. Determination of Phosphomonoesterase, Phosphodiesterase and Pyrophosphatase Activity.

It has been shown that bifidus possesses a type of phosphatase which acts specifically on α-casein of human milk and the following experiments were conducted in order to clarify this phosphatase activity. The activity of 3 types of phosphatases, monoesterase, diesterase and pyrophosphatase, towards synthetic organic substrates was examined at pH 4.8, 5.8, 6.2 and 8.6. The substrates were paranitrophenylphosphate, paranitrophenyldiphosphate and paranitrophenylpyrophosphate. With these substrates, inorganic P was not liberated at any of the above pHs. Phosphoserine was then tested as a substrate but in this case too, there was no liberation of inorganic P. These results suggest that the phosphatase of human Lactobacillus bifidus acts only on polymerized molecules of high molecular weight as the α-casein of human milk and is inactive towards synthetic substrates of low molecular weight. From this,

it is believed that this enzyme belongs to the group of phosphoproteinphosphatase.

B. Linkage Specificity of the Enzyme Fraction towards α-casein of Human Milk.

Bifidus phosphatase is believed to be a phosphoproteinphosphatase from its specific activity towards the substrates and the following experiments were conducted in an attempt to clarify the linkage on which it acts in the case of α-casein of human milk. Acid phosphomonoesterase was isolated from the human prostate, α-casein of human milk pre-treated with this monoesterase and then reacted with the bifidus phosphate fraction.

	1	2	3
α-casein of human milk (10mM casein P)	1.0	1.0	1.0
Prostate phosphatase	0.1mg	0.1mg	0.1mg
Veronal acetate buffer	0.5	0.5	0.5
	Left standing at 37° C		
	After 6 hrs.	24 hrs.	24 hrs.
Fraction B (1% solution)	0.5	0.5	0.5
	Left standing for 3 hours at 37° C		
	Inorganic P measured		

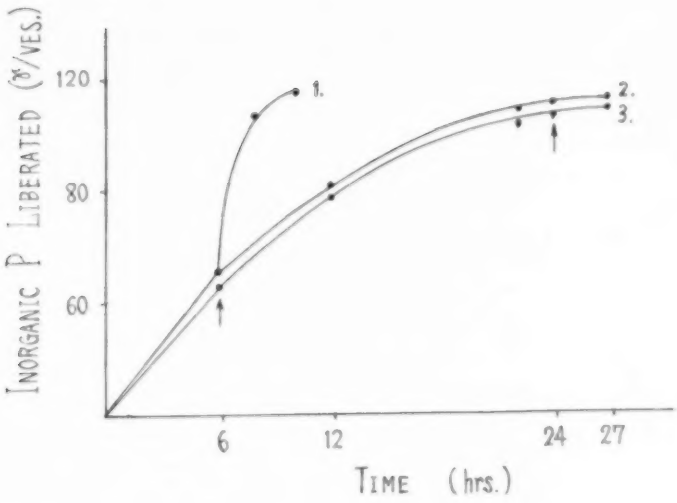
Human milk α-casein was reacted with prostate phosphatase for 6 and 24 hours, bifidus phosphatase then added and the inorganic P liberated was measured as shown above. A large quantity of P is liberated when the bifidus phosphatase is added after 6 hours but when it is added after 24 hours, there is no liberation of inorganic P.

Human milk α-casein was pre-treated with bifidus phosphatase and then reacted with prostate phosphatase according to the conditions given below.

	1	2	3
Human milk α-casein (10mM casein P)	1.0	1.0	1.0
Fraction B (1% solution)	0.5	0.5	0.5
Ascorbic acid	0.2	0.2	0.2
	Left standing at 37° C		
	3 hrs.	8 hrs.	8 hrs.
Prostate phosphatase	0.1mg	0.1mg	0.1mg
	Left standing at 37° C		
	Inorganic P measured		

When α-casein is first treated for 3 hours with bifidus phosphatase and then prostate phosphatase added, a small quantity of inorganic

FIG. 3



P is liberated but when pretreated for 8 hours, no significant finding.

According to Perlman, the P of the monoester link in α-casein makes up about 40% of the total P and this monoester P is completely liberated by reaction with prostate phosphatase for 24 hours. We obtained similar results in the case of α-casein of human milk. A characteristic of the bifidus phosphatase however, is the rapidity of the reaction when human milk α-casein is used as the substrate. This is shown by the sharp increase in liberated inorganic P when bifidus phosphatase is added after 6 hours reaction with prostate phosphatase.

The amount of P liberated at this time is about 40% of the total and there is no further liberation even when the reaction time is prolonged. On the other hand, when bifidus phosphatase is reacted first, the reaction procedes swiftly and all the P which will be liberated is promptly released so that there is no liberation when the prostate phosphatase is added. From the above findings it can be concluded that bifidus phosphatase acts on the P of the monoester link of α-casein of human milk. In other words, it should be called a phosphomonophosphoproteinphosphatase. Bifidus phosphatase moreover, acts only on the α-casein of human milk and not on the

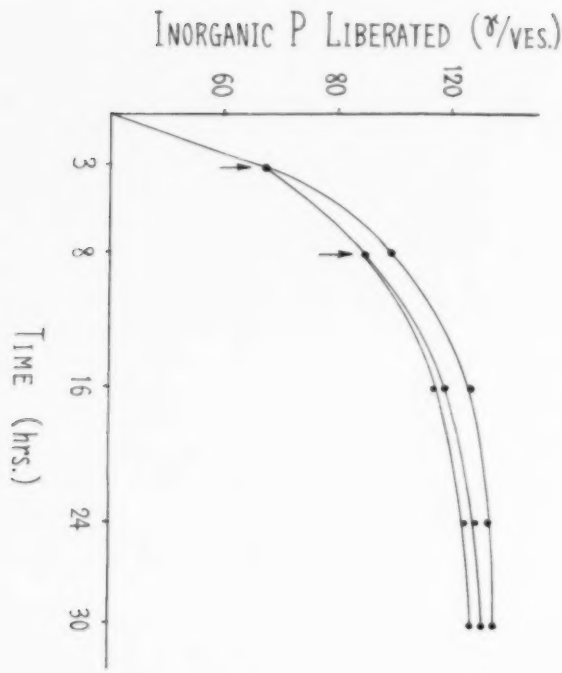


FIG. 4

β-casein so it is believed that it acts on the –O–P(=O)(–OH)–OH of the mono-

ester link and has no action on the –N–P(=O)(–OH)–OH link.

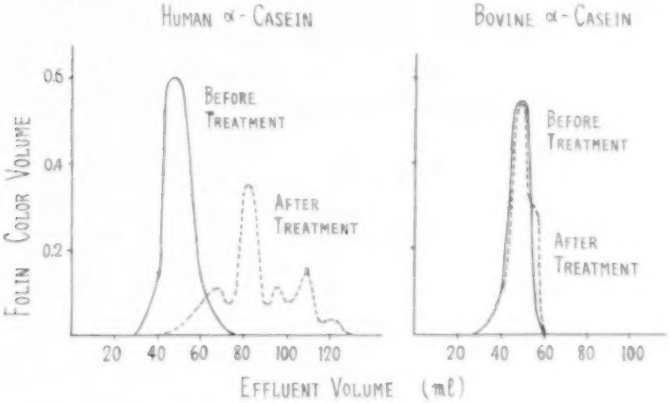
6. Alterations in the Electrophoretic Pattern of α-Casein of Human and Cow's Milk following Reaction with Lactobacillus Bifidus Phosphatase.

As repeatedly stated, the phosphoproteinphosphatase of bifidus acts only on the α-casein of human milk but in order to further verify this, the electrophoretic pattern prior to and after reaction was examined. It was found that there is little change in the pattern in the case of cow's milk α-casein but a marked alteration takes place following reaction in the case of human milk casein.

7. Enzymic Activity of the Various Strains of Lactobacillus Bifidus and Lactobacillus Acidophilus.

The phosphatase activity of 7 strains of Lactobacillus bifidus isolated from the breast-fed infant and 4 strains isolated from the calf was examined using α-casein of human milk and cow's milk as the substrate. It was found that the bifidus of breast-fed infants was highly active against α-casein of human milk while the bovine bifidus did not have a significant action against the α-casein of either human or cow's milk. Lactobacillus acidophilus was also almost inactive.

FIG. 5



8. Phosphoproteinphosphatase of E. Coli.

Experiments were conducted to see if E. coli, which forms the major part of the intestinal flora of artificially-fed infants, had an enzymic activity similar to Lactobacillus bifidus. E. coli (strain 16029) was treated in the same manner as the Lactobacillus bifidus and enzyme fractions prepared. Phosphoproteinphosphatase and phosphatase activity were examined with α-casein of human cow's milk and synthetic organic substrates. Significant findings were not obtained.

From the results, it is suggested that E. coli is unrelated to the mechanism of decomposition of α-casein.

DISCUSSION

As can be seen, a phosphoproteinphosphatase which acts specifically on α-casein of human milk was isolated from the cell body of Lactobacillus bifidus obtained from the stool of breast-fed infants.

	Strain No.	Rate of Activity	
		Human α-Casein	Bovine a-Casein
	1	42.3	1.2
Human	2	28.5	1.4
Lactobacillus	3	61.8	1.6
Bifidus	4	43.6	1.1
	5	51.3	1.9
	6	39.6	1.3
	7	51.2	2.1
	1	0.9	1.3
Bovine	2	0.78	0.85
Lactobacillus	3	4.2	4.6
Bifidus	4	3.2	6.3
Lactobacillus Acidophilus		1.1	–

It has almost no influence on the α-casein of cow's milk or phosphoserine. In other words, it acts only on phosphoprotein of high molecular weight and has no phosphatase activity towards synthetic organic substrates. The optimum pH is 6.1. The phosphorus linkage on which it acts suggests that it is a monoesterase and on the basis of its substrate specificity, may be considered a phosphoprotein-monoesterase. This enzyme is not found in E. coli and it also was found that the Lactobacillus bifidus isolated from the stool of nursing calves had no effect on the α-casein of either human or cow's milk. These findings are worthy of note as they not only indicate a type specificity between the bifidus in the intestinal flora of breast-fed infants and human milk, but suggest that the study of Lactobacillus bifidus and hence infant nutrition, should be reconsidered. The first problem which must be considered is whether merely converting the intestinal flora to a bifidus dominant—one without changing the quality of the milk preparation—will have a beneficial effect in the infant. If the activity of the bifidus is considered from the standpoint of intraintestinal infection and the flora made predominantly bifidus with the object of preventing growth of pathogenic organisms which invade the intestine, there would be no objection, but for this purpose, antibiotics suffice.

According to our results, the only way proliferation of bifidus in the intestines can have a beneficial influence on the protein metabolism of the infants is when human milk is made available and the administration of cow's milk would be without significance. Of

course, it is not clear yet, what significance the liberation of phosphorus of the monoester linkage has but it is not difficult to assume that when the phosphorus of α-casein is liberated, protein decomposing enzymes, especially carboxypeptidase, can act with greater ease. It can be seen that bifidus is closely related to the decomposition of protein of human milk. Reichelt[16] has shown that the bifidus has the same action of vitamin B_1 and suggests that vitamin B_1 was synthesized but Gerber, Schwartzer and others have stated that this is without significance as vitamin B_1 is not absorbed in the colon. The influence of bifidus on protein of human milk can be considered in the same way in the light of the present knowledge of intraintestinal absorption but the fact that bifidus is related only to human milk is important from the standpoint of infant nutrition.

The strain of Lactobacillus bifidus must be considered next. Besides the already known R– and S– strains, biological, morphological and serological differentiations are being carried out. György has isolated 4 strains and Petuely[18] has reported 3 strains and 3 types but these must be revaluated enzymologically. This investigation is only the first step in this field of study and too much cannot be said at the present time but it is believed that we have provided a scientific basis for the old saying "human milk is for the human infant and cow's milk is for the calf".

SUMMARY

Enzymological studies on Lactobacillus bifidus isolated from the stool of breast-fed infants showed that this bacillus acts only on α-casein of human milk. The significance is discussed.

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Clinico-Pathological Conference

MEMORIAL HOSPITAL, NEW YORK

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M. LOIS MURPHY, M.D., Presiding†

DR. MURPHY: Dr. Panidou, Assistant Resident, will present the case this afternoon.

DR. PANIDOU: This is a case of a 6 year old white female who was sent to Memorial Hospital with one month's history of fatigue and the onset of hemorrhagic pneumonia.

She had been well until the last two days in February when she complained of a sore throat and the physician found an inflamed throat and fever was 102. He prescribed combiotics and sigmamycin for 3 days and she responded. However, a "blood blister" on the lip was noted; the following day attention was drawn to ecchymoses on the legs thought to result from roller skating falls. Within one week of the onset of the sore throat, she was complaining of being tired continuously and was pale. There were occasional headaches. The findings were reported to be ulceration of the lip, dried blood in the external nares; the liver was 1 cm. below the costal margin and there were shotty lymph nodes.

She was hospitalized and treated with transfusions of fresh blood, Kenacort, 4 mg. per day, adrenal cortical extract, gamma globulin, and combiotics. After 6 days, she was discharged on Kenacort. In two days she was re-hospitalized because of hematemesis. Again transfusions, gamma globulin and combiotics were given for the anemia and low grade fever. Aristocort, 4 tablets every 4 hours and Ilotycin syrup. She improved slightly and was transferred to Memorial.

Past medical history: The child's birth was spontaneous. The weight was 8 pounds, 3 oz. and the neonatal period was normal. Her development was normal. She had varicella at the age of two and a half years. Respiratory infections occurred rarely. The only recent exposure to possible toxins was some Fuller's Spray on the family dog three weeks before her illness. The New York City Poison Control Center said a toxic agent was unlikely.

Family history: The parents were 33 and 34 years of age.

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There were two male siblings aged 14 and 12 years. The maternal grandfather had two or three facial skin cancers. The paternal grandmother had a history of healed tuberculosis.

Physical Examination: Weight was 34 pounds. Height 45 inches, blood pressure of 110/70, respirations 22 per minute, temperature 98.6. She was tired, pale, and irritable. The lips were crusted with blood. There were numerous ecchymoses over the body both spontaneous and secondary to injections and venipunctures. The tip of the tongue had an ulceration, 0.5 centimeters. The teeth were carious. There were petechiae on the tonsils. The heart and lungs were normal. The abdominal examination revealed the liver to be two centimeters below the costal margin but the spleen could not be palpated.

In addition to the ecchymoses, the skin showed petechiae over the chest and extremities. There were healing ulcerated areas of the inner aspect of the right calf and the right wrist.

Course in the hospital: The patient received transfusions of fresh blood, intravenous prednisone and ACTH, 2 million units of penicillin and tetracycline. The bleeding paused temporarily and she appeared improved for a period of about a week when a painful swelling of 1 cm. was noted on the right calf. The following day she complained of abdominal pain, vomited red blood and passed tarry stools. This continued over the next three days and hematuria was noted as well as temperature elevation to 103 degrees. She began to complain of intermittent abdominal pain which was more marked in the right lower quadrant. The pain was exaggerated on deep inspiration and coughing. The respirations were 36 per minute, coarse breath sounds, with moist rales were heard over the left lower lobe posteriorly. The abdomen was slightly distended. A Gastric Service consultation reported that the rectal examination was negative, but there was diffuse abdominal tenderness without rigidity.

The abdomen was distended and the feces were black. The surgeon felt that the possibility of a pathological lesion responsible for the melena was far outweighed by the severity of the operative risk.

She continued to complain of abdominal pain, passed tarry fecal material, vomited blood and ran a spiking fever. She continued to receive blood transfusions, anti-biotics, adrenal steroids as well as vitamin K and Premarin in an effort to control her bleeding. Her abdomen became distended and tense. Pulmonary rales increased. Heart failure developed which was treated. The hematemsis per-

sisted. The fever rose up to 105.6. She was on the 13th hospital day about one month following the onset of symptoms.

X-ray studies: The skeletal survey. There is evidence of demineralization of all of the bones. The chest is negative. Chest: pneumonitis of both lungs. Abdomen showed considerable gas in the small and large bowel without distension. No obstruction.

Laboratory studies: Bacteriology: Nose and throat cultures grew a few Staph aureus, Staph albus, Coli Areogenes. Blood culture taken on admission was negative. One taken the day before death contained four colonies of B. pyocyaneus per cc of patient's blood. This organism was partially sensitive to chloromycetin but resistant to others routinely tested.

Heterophile antibody titer was 1:14. Coombs direct and indirect tests were negative. The peripheral blood: On admission hemoglobin was 11.7, WBC 2,600, Platelets 35,000.

At the time the child was improved, the hemoglobin was 12.4, WBC 5,400 and Platelets 55,000. Just prior to death, the hemoglobin was 8.9 and WBC 500.

The urine was essentially negative except for many large red blood cells.

Biochemical: On admission, Bilirubin was .61, Cephalin 1 plus, .22 Thymol. Protein 8., Albumin 3.9, Uric Acid, 3.4, BUN 15.

Prior to death Bilirubin was .68, Cephalin was 3 plus. Thymol. was not done. Protein 7.2, Albumin 3.6, Uric Acid 2.6, and BUN was 9.4.

Bone Marrow: Three specimens (all after treatment) were hypocellular, showed no megakaryocytes, a few granulocytes, a few erythroid elements, lymphocytes and plasma cells specimen was considered too scanty for diagnosis.

Now, I think in this case which is characteristic, the most pronounced symptoms are: anemia, hemorrhage, and infection. When we have these three, hemorrhage, anemia, and infection, we usually have the features of bone marrow failure. Even after treatment one specimen was very hypocellular, and I don't think the treatment could cause that hypocellularity of that bone marrow because the child had been on ACTH and steroids. There was no chemotherapy done. There was no irradiation done, and so the whole picture I think is a case of aplastic anemia.

Aplastic anemia can be caused by drugs, by irradiation. It could have been caused by infection, or it could be an idiopathic aplastic anemia or it could be leukemia.

In this particular case the infection could be narrowed because

of the history. The child was not sick for a long time. She was just sick for a month. The hemorrhagic phenomenon started immediately after the onset of the disease. The petechiae was present and ecchymoses were present at that time.

The main features for aplastic anemia here were the enlargement of the liver and lymph nodes, the child had hemorrhagic phenomenon, low WBC's, low hemoglobin, low platelets, and the bone marrow is hypoplastic. Also the x-ray findings of demineralization of all bones does go with the diagnosis of aplastic anemia because we have a diffuse osteoporosis.

Another thing that could cause aplastic anemia is a toxic agent. I don't know how accurate this is—but the child was exposed to Fuller's Dog Spray about three weeks prior to the onset of the disease and some of the constitutents of this spray are known to be toxic to some humans, and could cause nausea, vomiting, irritation to the skin, and death in this case could be caused by a respiratory failure. Also rotenone has the same effect, in that it has been known to cause vomiting and also gives bleeding in the patient, and all these are given to us by studies. There have been only a few cases. Sometimes these inert ingredients can give toxic effects to human beings and reported cases show bleeding in bone marrow, bleeding in spleen and central nervous depression. So, this could have been but I'm not sure if it was.

Then, the second choice was idiopathic aplastic anemia and the third source was aleukemic or subleukemic leukemia.

There is another disease that could cause aplastic anemia, but we'd have to have a few more signs to get a diagnosis, and this is Reticuloendotheliosis. This might have depression of the bone marrow, with enlargement of both liver and spleen, and certain changes that were not present in this case.

Another choice might be bloodstream infections which sometimes give aplastic anemia, but the bone marrow again is cellular, and the spleen is enlarged.

Several tumors could cause aplastic anemia when they involve the bone marrow but in this case you have nothing to go with it. At the beginning the disease was very acute and killed the child about a month after the onset of it.

So, I think the first choice is aplastic anemia due to toxic agent, and then leukemia and aleukemic leukemia.

QUERY: If you care to, I'd like to have you say something about the chain of events. Would you describe the reaction of the drugs such as Premarin.

DR. PANIDOU: The child was bleeding in the intestinal tract, with hematemesis, abdominal pain, high fever, at the end. If anything local in the abdominal cavity was causing this, it could have been shown by the x-rays, but there was no sign of obstruction.

DR. MURPHY: Dr. Panidou I'd just like to ask you for emphasis: in all these diseases which you considered in your differential diagnosis, which one gave you the most trouble? You gave a nice long list but which disease that we see could most likely give you this picture other than your diagnosis of idiopathic aplastic anemia.

DR. PANIDOU: Leukemia.

DR. MURPHY: I want to remind you that all the bone marrows that were reported here were treated bone marrows, and as you know the earliest manifestation of a response to steroid therapy (and this child had considerable steroid therapy) is depression of the peripheral white count and also a depression of the leukemic cells in the bone marrow; so that it is not entirely safe to rule out leukemia on the basis of treated bone marrow.

You will recall when Dr. Ley, our hematologist, is asked to give an opinion on one of these patients with deficiency of cells, and doesn't know whether we obtained a diluted specimen or whether there's really nothing there, or just what the problem is, he encourages them to send for the marrow that was taken before any treatment was given. I think an important point to keep in mind is that when you interview a new patient, if a marrow has been done before the steroids have been started, it is important because Dr. Ley will not give an opinion usually on a treated bone marrow.

DR. PANIDOU: What about the "meta" cells?

DR. MURPHY: In aleukemic leukemia there wouldn't be any there. The only ones would be the leukemic cells which would get depressed to a hypoplastic state, if the patient simultaneously develops a severe infection. Where he cannot respond, this may be the state of his death with a hypoplastic marrow.

Under these circumstances, the hematologist usually will request biopsy of the bone marrow so that we can find out what is there. The child was infected and bleeding and it was not considered safe to open the bone and this is usually the picture that we're faced with.

The other members of the House Staff had an opportunity to look at this case before they came. We've asked them to think about it, and I'd like to ask if there are any additional comments

that anybody on the House Staff would care to make.

Dr. Arnow, no doubt you're thinking of something important.

DR. ARNOW: I just wanted to say that it was a very good discussion I think—on the differential diagnosis, and I have nothing to add especially.

DR. MURPHY: Dr. Psarrau?

DR. PSARRAU: I have the same point. It's hypoplastic anemia due to chemical agents.

DR. MURPHY: We checked with New York City Poison Control Center and they said there were no other reports of this; apparently this is a popular dog spray and they reassured us that they did not think this was contributing to the patient's disease because they had no other history of such occurrence. It doesn't rule it out, but sort of lowers it on the list.

QUERY: Does she have some special sensitivity?

DR. MURPHY: It's possible.

Dr. Aguila?

DR. AGUILA: My first impression is leukemia because I think this poison control center is very reliable. We always use it for problems and I'm sure about their reliability. I have investigated this.

DR. ARNOW: It didn't have to be that particular toxin. It could be idiopathic.

QUERY: The bone marrow didn't have any blasts?

DR. MURPHY: Well, many times we do several bone marrows and they are diluted specimens and they're not satisfactory, so you can't rule the disease completely out on the basis of bone marrow.

DR. PANIDOU: We didn't have any peripheral blood to see how the cells looked in the peripheral smear, whether it were hypochromic or microcytic anemia as far as red cells are concerned and if it was monocytic or lymphocytic.

DR. MURPHY: Now, I'd like you to think a little more about the terminal events in the hospital.

QUERY: I think she overlooked in the discussion, the x-ray of the chest.

DR. PANIDOU: That was a pneumonitis.

QUERY: There were two x-rays or is there a slight inaccuracy in the case?

DR. PANIDOU: The first x-ray of the chest was negative on admission. Later on, at the time she was having respiratory difficulties, there was pneumonitis in both lungs. The chest at the time the skeletal survey was taken was considered negative, but later

on, at the time we took the flat plate of abdomen, there was pulmonary inflammation. Could it be an infection?

DR. MURPHY: That is right.

QUERY: How about some inflammation in the intestinal tract, secondary to steroid?

DR. MURPHY: This is a picture that we frequently see in a terminal case, no matter what it is: nonresponsive, leukemic, aplastic anemia, and I notice also that there's a little mistake in the surgeon's consultation where he said the possibility of a pathological lesion causing the melena—a surgically approachable lesion causing the melena—was overshadowed by the risk.

DR. PANIDOU: Was anything found?

DR. MURPHY: The surgeons did not think the risk of exploration was worth it, but they did not suggest a specific surgical lesion. They couldn't put their finger on it, but they thought if they were to do an exploratory just to find out, the risk was not justified. They did not have a specific recommendation at that particular time.

Dr. Goldfarb?

DR. GOLDFARB: I have not really much to add except I was impressed by the x-ray which said demineralization of all of the bones, and that plus all the generalized ecchymoses makes it a generalized disease which is suppressing the bone marrow.

DR. MURPHY: Yes, Dr. Arnow?

DR. ARNOW: Was demineralization secondary to the steroids?

DR. MURPHY: Yes, I think this is a possibility, Doctor. It might explain this. There is nothing specific which indicated a metastatic lesion in the bone. There are usually leukemic bands but this is a very short illness so it can be just dilatation in the child.

Dr. Franklin, do you have any points to raise?

DR. FRANKLIN: (Associate Attending Pediatrician) No. We saw a small girl who came in here with leukemia, having been on steroids from the January before until she came in, and we were unable to make a diagnosis through June, July and August; it took a whole year before the diagnosis of leukemia could be made and she'd been on steroids.

So I don't think you can rule out leukemia. I think the aplastic would be more unknown. I don't know about a perforation. There is none here in the flat plate of the abdomen, but I would assume there was probably some bleeding into the abdominal area some place, secondary possibly from other parts of the body into the

abdomen, and pneumonitis present. I think it's too much of a generalized disease to guess. Also the first plate of the chest was negative so cirrhosis would probably be ruled out any way from the general course of the disease.

DR. MURPHY: Dr. Dargeon?

DR. DARGEON: I'm just wondering—unfortunately we'll probably never know in this country now, what happens to the bone marrow in these bacteremias which we know can be clinically submerged any way by using the antibiotics and the steroids. In the old days we used to consider that these children died from an overwhelming infection. We never had enough bone marrow to know whether they had a hypoplasia or aplasia at the time. There are some suggestions here that some microbial action could have been going on for all this period of a month when the child was ill.

She had combiotic and sigmamycin just for three days, then she apparently developed hemorrhagic phenomenon quite promptly, within maybe the next week or 10 days as indicated by the transfusions of fresh blood, so that she was really in an acute phase of hemorrhagic diathesis at that time and she still had further steroid to again maybe submerge the clinical signs.

There are some ulcerated areas on the inner aspects of the right calf and right wrist, which might have been the result of ecchymoses or petechiae or maybe bacterial emboli. We don't know. I think the evidence, of course, is that this bacterial problem of which we have testimony in our laboratory studies here (not too significantly until just before death actually) showed pyocyaneus. I think most of the evidence is in the area of a hematopoietic disaster with infection engrafted on it, which is shown in the course with the pneumonitis. I agree that this terminal event had, if not at least hemorrhagic background, a fairly conspicuous place in the foreground. Whether or not the drugs were accountable for ulceration in the bowel or whether bacterial emboli had accounted for some bleeding within the abdominal cavity—or as Dr. Franklin and others have suggested that she just bled from some point within the abdominal cavity without perforation is, I think, to be seen; she didn't have any air in her abdominal cavity so we can assume she didn't have a perforation of the gastro-intestinal tract. I don't know if an LP was done here?

DR. PANIDOU: No it was not apparently considered indicated.

DR. MURPHY: I'm a little disappointed that you didn't take more seriously the right lower quadrant pain she had. We see a

lot of patients with bleeding but the pain may be diffuse and bleeding may be of upper epigastric type with the diffuse bleeding which we see; and also the character of the septicemia, which she developed on the last day, which was not present when she came in, so it was something associated with this terminal event, which, it seems to me was caused by an intestinal kind of organism. The sensitivities for this organism were not reported until after she died and she had not received chloromycetin but she received tetracycline. Any more discussion before we decide what happened? We have two things to decide on, the primary disease and cause of death.

Dr. Panidou's primary diagnosis is: aplastic anemia and the cause is toxic. Any comment? Did you change your mind?

DR. PANIDOU: No but I'm not quite certain.

DR. MURPHY: How about the next one?

DR. PANIDOU: The next one would be hemorrhage, appendicitis.

DR. ARNOW: My first choice is idiopathic aplastic anemia. The cause of death? I want to guess that there was gastric perforation, and hemorrhage and peritonitis, a combination of hemorrhage and infection in the peritoneal cavity being the major causes.

DR. MURPHY: Dr. Psarrau?

DR. PSARRAU: Aplastic anemia; and the cause of death is massive hemorrhage, and a possible perforation.

VOICE: Leukemia is my first diagnosis. Cause of death is hemorrhage—that is hemorrhage secondary to perforation.

VOICE: My diagnosis—Aleukemic leukemia; and cause of death: hemorrhage.

DR. GOLDFARB: Aleukemic leukemia, and I'd like to suggest the possibility that this child had a ruptured appendix which might have led to a large hematoma in the right lower quadrant rather than the usual appendiceal abscess.

DR. FRANKLIN: Aplastic anemia, idiopathic and pneumonitis and hemorrhage and perforation.

DR. MURPHY: They never die from just one thing do they?

Dr. Dargeon?

DR. DARGEON: Aplastic anemia accompanied by sepsis. While I'd like to accept the possibility of aleukemic leukemia, we just don't have enough positive evidence in here to put it down except as a maybe. So if you put down sepsis, I think it probably includes it, the anemia and some of these terminal events which could be associated with a hemorrhagic diathesis. Pneumonitis is one and

there may be other points of foci or emboli of the bacterial sepsis, which might have produced the perforation elsewhere.

Dr. Murphy: I think that's a good possibility. All right, any more discussion? We'll hear from our pathologist, Dr. Hartman.

Dr. Hartman: This child had aplastic anemia, the etiology of which is completely undetermined. At autopsy the findings which were of considerable interest were: a totally necrotic appendix and a terminal ilium, numerous bacterial colonies scattered throughout all five lobes of the lung and foci of hemorrhage into the cerebral system. There was no gastro-intestinal bleeding at autopsy. There were microscopic manifestations of shock in the kidneys and heart, and there was a considerable degree of cerebral edema. I say aplastic anemia with a certain degree of assurance. I have in front of me the report of Dr. Ley dated March 18th and the marrow was done in Florida on the 6th. This was the day the child was originally admitted to the hospital for the first time; he felt this is not what one would expect with any form of leukemia, but is consistent with either aplastic anemia or conceivably some form of infection from unsolved tumors. So the finding seen in the marrows *following* treatment was also the finding seen in the marrows *prior* to treatment, and that we would have to accept it as an aplastic anemia and not a leukemia. As far as the etiology of aplastic anemia is concerned, I think we'd best put it into the idiopathic group as we have nothing that we can incriminate as the causative agent here. Referring again to the dog wash or dog powder—whatever it is—I think Dr. Murphy's investigation from the Poison Center that this could not be the etiology, is probably something we'll have to accept.

It's always interesting to speculate what else the child might have been exposed to. I'm sure there are any number of thousands of things that could cause this. But in looking through the chart, I discovered that her father works for something called, "Radiation, Inc.", and my overactive mind wondered if maybe the child (I don't know what "Radiation, Inc." is) had been taken there as fathers will, to see "the place where Daddy works" and possibly been exposed to radiation; while we could never substantiate it, this certainly represents a rather exciting possibility.

Dr. Arnow: Or some substance could have been brought home in his work clothes. There was an article in "Life" a couple of years ago, about a plant in Tennessee where they were working on radioactive by-products; they discovered two workers had brought home contaminated clothing.

DR. HARTMAN: As I say, I don't know what "Radiation, Inc." is but it is a very exciting title. I don't have very much else to say.

The autopsy was reasonably straight-forward. The marrow at post is an extremely hypo-cellular marrow with no evidence of hematopoiesis whatsoever. There are just isolated focal accumulations of plasma cells and some small degenerated cells that I was totally unable to identify or even guess at their origin; also, the lymph nodes and the spleen and the liver showed no evidence of extra-medullary hematopoiesis, which to my mind would be compatible with some severe hematopoietic depressing agent. There is a tremendous amount of reticulum cell activity scattered throughout the lymph nodes, but again I could not find in rather careful study of many of the nodes, any attempt at hematopoiesis

The microscopic picture of bacteremia and bacteria in an aplastic patient was well shown. I do not believe all the bacteria and necrotic tissue that we saw could be due to post-mortem decomposition, but rather must be accepted as a terminal event. The child was posted 8 hours after death and while we do see some changes, they were not manifested in the sections that I had at my disposal, so to reiterate, I think the child had an aplastic anemia, idiopathic type. The terminal event would probably be acute appendicitis and severe bacteremic pneumonitis and just to complicate a specific choice there were focal cerebral hemorrhages and a considerable amount of cerebral edema for a 7 year old child.

DR. DARGEON: Could you ascertain, from a chronological standpoint whether this was present for some weeks or was it just terminal.

DR. HARTMAN: No, I would think that this was something that would have to be dated in hours at the most.

DR. DARGEON: In hours?

DR. HARTMAN: Yes, she didn't have any cells to react with and so the landmark that we usually use for dating things is completely gone. I would think if it were much more than a few hours' time, it probably would have perforated. As it was, all lymph nodes draining that area were extremely large, necrotic and suppurant, so it was something I would think was hours, not minutes, and not days or weeks.

DR. DARGEON: You couldn't do anything about that?

DR. HARTMAN: No.

DR. DARGEON: So, it wouldn't be the immediate cause of death—just one of multiple—just one on the broad side.

DR. HARTMAN: That's right.

DR. DARGEON: I don't want to stop anybody but I'd like to ask you about those lesions of the skin—did we have any post mortem material on the skin lesions?

DR. HARTMAN: There were no skin lesions described. An ulceration was noted in the mucous membranes of the mouth and the oral pharynx.

DR. ARNOW: The patient was bleeding from somewhere along the g.i. tract. Did they inspect the mucosa along the alimentary tract?

DR. HARTMAN: They reported petechial hemorrhages in the upper jejunum and the upper ileum.

DR. ARNOW: These petechial hemorrhages, if you get enough of them could they account for any considerable amount of blood to produce hematopiesis and tarry stools?

DR. HARTMAN: We see a lot of melena in patients that demonstrate no other lesion at autopsy other than just petechial hemorrhages. I think it's rather important. I mean judging from the gross picture, one would expect some large ulcerations, but not necessarily. Of course we get these extremely large ecchymoses in the skin and with probably minimal points of bleeding in the blood vessels—they'd probably be microscopic, I guess, if we had gone right down to it, instead of being extensive areas of the geometric pattern anyway.

DR. MURPHY: I would like a little review of the pathological diagnosis of aplastic anemia. It's the absence of haematopoiesis in the marrow.

DR. HARTMAN: We thought the term aplastic anemia morphologically means nothing. There's nothing to see really. You see a fatty marrow with isolated reticulum cells and usually isolated plasma cells. We see varying degrees of the absence of normal constituents of marrow: and in searching three slides in this child this afternoon, I could find no megakaryocytes, and no evidence of erythropoiesis, and no evidence of myelopoiesis.

The finding of plasma cells and reticulum cells is a finding that has been duly recorded many times in regenerating marrows, following severe irradiation, both in animals and in humans, and this phenomenon of plasma-cytopoiesis or reticulum cell proliferation can reach the point where a diagnosis of reticulum cell sarcoma or myeloma will be sincerely and honestly entertained on regenerating post-irradiation marrow.

For some reason or other, I don't believe anybody knows why, the plasma cell is a hearty cell and it apparently regenerates quickly.

As for the etiology of aplastic anemia, clinically, I'm sure you people know more about it than I do. The biggest group of the aplastic anemias are the idiopathic ones, the ones for which no etiology can be discovered.

There have been many, many drugs, toxic agents, a host of other things that have been incriminated in various numbers of clinical cases, ranging all the way from solid metals to drugs that are used routinely from the point of view of treating epileptics, and I'm afraid we could not incriminate any specific thing in this case. There is just nothing we'd have to base incrimination on, and we would have to sign it out as idiopathic aplastic anemia with pneumonitis, appendicitis, sepsis and hemorrhage.

DR. MURRAY: You would not have difficulty in diagnosing aleukemic leukemia if you examined the lymph nodes, spleen, and liver. You'd find leukemic cells there even though we may not have gotten good marrow aspiration. This is not a problem at autopsy.

DR. HARTMAN: No, that's not necessarily true. Some of the leukemic patients that come to autopsy, particularly from institutions such as this, are extensively treated. At autopsy, they do not look like the classic leukemic picture as previously described 20 years ago, and on a gross diagnosis (we have a lot of trouble sometimes in making a diagnosis of leukemia) and even microscopically, the diagnosis can be made only with great difficulty.

Usually there is at least some evidence that there was a leukemic process going on prior to the patient's demise, and it's just a matter of interpretation of bizarre looking cells, so we're perfectly willing to go along with the clinical diagnosis of leukemia.

In this case, I think that Dr. Ley's interpretation of the marrow (which by the way, was a possibility entertained by original review of the marrow in Florida), that the child did have aplastic anemia and not aleukemic leukemia, is the one on which we would have to lay considerable weight and base our judgments accordingly.

DR. MURPHY: Did he terminate his report by asking for biopsy? As I recall that was the case.

DR. HARTMAN: Yes, he did. And furthermore, if any more has to be added, in seeing the patient on the 28th, he felt that this could only be aplastic anemia and not leukemia, he had by that time seen the previous marrows, so it was a considerable degree of hindsight.

DR. MURPHY: Were you ever sure that it's not leukemia that was secondarily infected?

DR. HARTMAN: Yes, I think it's perfectly true despite the reverence we do hold for the first diagnosis in Florida and Dr. Ley's

support of it. We still don't know because we've had leukemias here with aplastic anemia. This child did not live long enough following the initial syndrome time to demonstrate what we have seen here in huge number, enough children to make us very leary about making an unequivocal diagnosis of idiopathic aplastic anemia until we have observed the child for some time. Of course, we're up against it from the therapeutic standpoint and it's very difficult because if we don't treat the child rather vigorously with steroids we do have the difficulties of aplastic anemia; if we do treat them, we mask our diagnosis frequently; and in this case, if there was infection, either it was going on or caught up with the child before a definite decision could be made as to whether it was aleukemic leukemia or aplastic anemia. I think on the basis of what we have here, we can't go any further than leave out the diagnosis of aleukemic leukemia.

Just let me add one more thought to the confusion. The organism that was cultured from this patient's blood the day before she died was pyocyaneus and while no cultures were done at autopsy the morphology, as seen in the slides, is compatible with a rod-shaped organism which pyocyaneus is and so I have no qualms whatsoever about accepting that as the organism we see throughout the tissues.

Many cases of pyocyaneus septicemias have come to be reported recently in the pathology literature, and these cases interestingly enough, are characterized by a leukemoid reaction, so as you say had the child lived a little longer, the chances are she might have developed the leukemia which we were all looking for.

Dr. Pandou: Sometimes aplastic anemia is in the idiopathic group. One is in the idiopathic group and the other is a pre-stage of leukemia.

Dr. Murphy: That's right. I think there are certainly a number of children each year that present this picture and pursue this course. We still do not know—until not a single cell is found that looks like a leukemic cell at microscopic examination—and then we assume it is aplastic anemia; but I certainly cannot tell which one it is going to be and I don't know how.

Dr. Hartman: I'm sure we can't either.

Dr. Murphy: And I don't think biopsy of the marrow would necessarily help us.

Dr. Hartman: It would help from the standpoint of substantiating the aplasia of the marrow. I mean whenever you do a marrow smear you always have a suspicion that maybe this is not an

adequate aspirate and a biopsy can do nothing more than to show you that this is the true state of the marrow from the cellularity level. It won't certainly identify the cells, particularly on a section, but it will tell you whether the marrow is hypo-normal or hypocellular; from the point of view of substantiating a diagnosis of aplastic anemia it is important, but it certainly can't help you in telling whether this patient is one that is going to become leukemic or not. That we have no help for.

DR. DARGEON: Apropos your remarks about leukemoid reaction occurring with some of these gram negative rods, have marrow tests been done too, which show the activity of the immature rods or are these mostly on peripheral blood tests?

DR. HARTMAN: No, I know of two cases, Dr. Dargeon—one in a child and one in an adult, both of which were severely hyperplastic marrows and in both, the diagnosis of leukemia was sincerely and honestly entertained prior to the demonstration of an overwhelming Pseudomonas pyocyaneus infection, and I don't know how you can tell. So far as I know, alkaline phosphatases were not done on the marrow cells so that I know of no way other than that of telling whether it represented a true leukemia with an associated infection, or whether it represented just a primary infection with severe marrow response.

Current Literature

Edited by

MICHAEL A. BRESCIA, M.D.

Röntgenanatomie der Neugeborenen—und Säuglingslunge. By Dr. Z. Zsebök and Dr. R. Glauner. Cloth. Illustrated. Pp. 160. Price $16.05. Stuttgart, Germany, Georg Thieme Verlag, 1958.

This book presents a valuable tool to the pediatrician, the radiologist and the physician specializing in chest diseases. It aids them in the daily problems of chest pathology with which they are confronted. The volume contains a detailed analysis of the X-ray anatomy of the bronchial tree, of the vascular system in the lung and of the thymus as well as of changes after the fetal period. The book is well written and is illustrated with a large number of excellent pictures and radiographs. It is one of the best monographs available on the fundamentals of the radiological anatomy of the lungs of the newborn and infants. J. SMULEWICZ, M.D.

ANOMALIES OF INFANTS AND CHILDREN. BY D. MCCULLAGH MAYER, D.D.S. M.D., F.A.C.S., F.I.C.S. AND WILSON A. SWANKER, M.D., F.A.C.S., F.I.C.S. Cloth. Illustrated. Pp. 454. Price $12.00. New York. McGraw-Hill Book Co., Inc. 1958

The main purpose of this book as the authors state in the foreword is to help "those who are interested in this subject to discuss intelligently with the parents and others concerned the anatomical anomaly from which the patient is suffering, the resulting physiologic disturbance, the rationale of treatment, and the accepted time for repair". The authors have accomplished a creditable work as far as they went. Practically half of the book is devoted to anomalies of the head and neck. Albeit, this is a most important area from a cosmetic standpoint, nevertheless more space should be found for other anatomical locations which were sadly neglected. Very little space is devoted to the vast number of anomalies of the gastro-intestinal tract and the cardio-vascular system. The reader will find little information as to the timing of surgical repairs of these two important systems. The space taken up by the surgical techniques of skin grafting and the chapters on burns in childhood and accidents although interesting and conducive to producing anomalies do not properly belong in a book which the authors

themselves state is for "quick reference". This reviewer does not wish to be too critical since this is a most valuable work. The embryological explanations of the anomalies are well done. If the next edition should make some of the changes in subject matter as indicated, it will indeed then become a valuable text for "quick reference" for practically all anomalies. M. A. B.

Klinische Funktionsdiagnostik. By DR. H. KUCHMEISTER, DR. W. BOLT, DR. H. GOLDECK AND DR. H. HAMM. Cloth. Illustrated. Pp. 445. Price $11.50. Stuttgart, Georg Thieme 1958. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

The purpose of this book is to compile in one volume functional tests used in the diagnosis of various clinical disorders. No attempt was made to cover in detail all available tests but only those which have proven of value to the author and his coworkers. In this second edition, the most recent advances in functional tests—both in the laboratory and at the bedside—are described and evaluated critically. This necessitated discussion of the physiological functions of many organs as a pre-requisite to the understanding of abnormal reactions. There are chapters on functional tests in the diagnosis of endocrine disorders, diseases of the cardio-vascular system, of the respiratory tract, blood, kidneys, gastro-intestinal tract, liver and pancreas as well as metabolic dysfunctions. The tests which are of actual importance for the functional diagnostic in the clinic are outlined concisely. The bibliography is ample and the charts and illustrations should help in the understanding of some difficult tests. Although primarily written for those engaged in internal medicine, the pediatrician will find a variety of special tests which are of value in the clinical diagnosis of pediatric disorders. M. WEICHSEL, M. D.

LEVINE, S. A. AND WOODWORTH, C. R.: Congenital Deaf-Mutism, Prolonged QT Interval, Syncopal Attacks and Sudden Death. (New England Journal of Medicine, 259:412. August 28, 1958)

The authors report a case which seems to be a distinct clinical entity. Its features are congenital deaf-mutism, peculiar EKGs, inconstant in form with long QT intervals and large, notched T waves, syncopal attacks and sudden death early in life. Although it is suspected that the underlying cause is a metabolic disturbance in the cellular electrolytes or in enzyme behavior, no satisfactory explanation of the condition is apparent at present. M.A.B.

A Bibliography of Internal Medicine—Communicable Diseases. Edited by ARTHUR L. BLOOMFIELD, M.D., pages 538, cloth, University of Chicago Press, Chicago, Illinois, 1958, Price $10.

The surge of new knowledge in medicine has created a tremendous problem. The student tends to keep up on the new literature at the expense of the fundamental and the historical. The author has compiled a definitive and exhaustive bibliography of communicable diseases with excerpts from practically every important reference since 1800.

It is fascinating to read medical writings of 100 years ago and to realize how keen clinical insight and incisive style of writing enabled the clinicians and investigators of yesterday to report their experiences so vividly. Handicapped by a paucity of knowledge in basic sciences and lacking the array of diagnostic aids that are now available, these physicians none the less came close to many truths—in numerous instances, as close as we are today.

Dr. Bloomfield has skillfully combined the old with the new literature in his new approach to medical history, bringing together the best medical writing on the subject of communicable diseases. For the physician interested in what the older literature had to say and for the student, general practitioner, and specialist interested in a stimulating review of internal medicine and communicable diseases as reported from about 1800 to the present day, this volume is a welcome contribution. JOSEPH M. COVELLI, M. D.

DE MOWBRAY, R. R. AND BISHOP, P.M.F.: Management of the Undescended Testis. (British Medical Journal, 5084:1367, June 14, 1958).

A follow-up study of 209 patients with undescended testes is presented. The importance of assessing the initial position of the testis in regard to the choice of treatment is stressed. Hormonal treatment with chorionic gonadotrophin is successful in bringing down more than 60% of a selected group of undescended testes. There is no evidence that chorionic gonadotrophin in moderate dosage can cause permanent damage to the seminferous tubules. Orchidopexy is the treatment of choice when there is a mechanical defect or when chorionic gonadotrophin fails. Hormonal and surgical treatment should take place about the age of 9 or 10. Assessment of fertility in 24 patients with bilateral cryptorchidism reveals that 70% of them have a normal degree of fertility 10 years after treatment. AUTHOR'S SUMMARY

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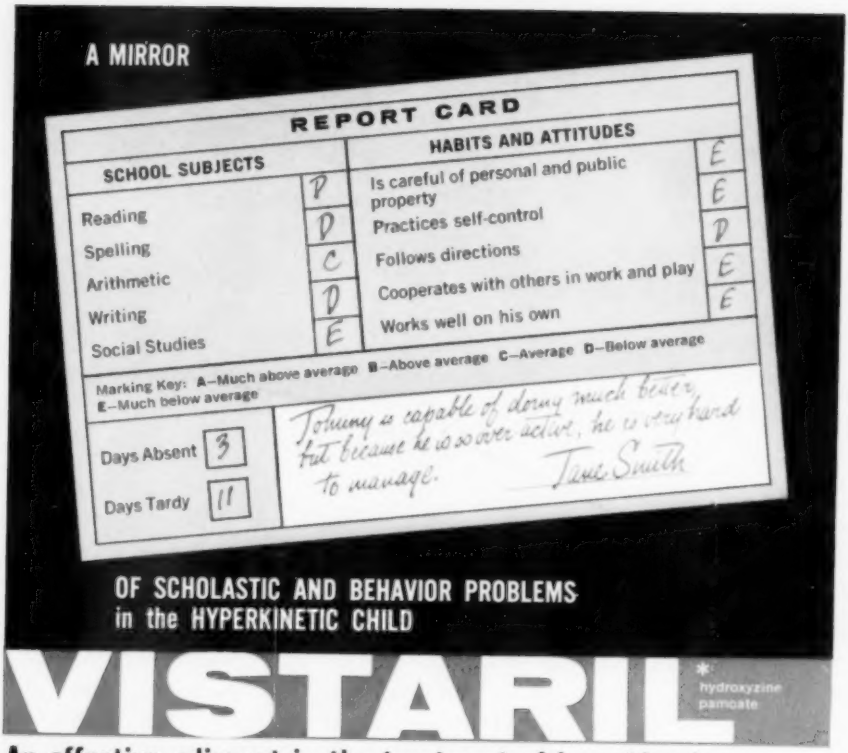
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